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(54) Title: TREATMENT OF INSULIN-RESISTANT DIABETES

(57) Abstract

Insulin-like growth factor (IGF) is used for treatment of type A insulin-resistant diabetes by reduction of glucose levels. The treatment is applicable to Mendenhall's Syndrome, Werner Syndrome, leprechaunism, lipoatrophic diabetes, and other lipoatrophies.

* See back of page

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TREATMENT OF INSULIN-RESISTANT DIABETES

Technical Field

The present invention relates to the treatment of insulin-resistant diabetes. In this rare condition, hyperglycaemia (elevated blood glucose) does not respond to administered insulin, possibly due to a genetic abnormality in the cellular insulin receptor which prevents insulin from performing its normal role.

Background

The syndrome which bears his name was first described by Mendenhall in 1950 in three children from one family. All developed insulin-resistant diabetes when aged about 7 years and subsequently died in ketoacidotic coma. Several constant somatic abnormalities were noted, including early dentition, facial dysmorphism and tonsillar hypertrophy which predisposed to the development of middle ear sepsis. The children had enlarged external genitalia with abdominal protuberance and in common with other insulin-resistant states, acanthosis nigricans was observed. Pineal hyperplasia was found at post-mortem, the cause remaining obscure.

In 1975 the syndrome was described in two siblings from a family in the UK. One died at the age of 7 years, in the other, emergency hypophysectomy was performed and proved to be life-saving when the child developed

ketoacidotic coma. The cause of insulin-resistant diabetes in this distressing syndrome was subsequently examined by Taylor et al in a further patient and marked decrease in the cellular binding of insulin was demonstrated by in-vitro culture of cell lines from the child. Thus Mendenhall's syndrome is regarded as analogous to other rare forms of diabetes with acanthosis nigricans, i.e. type A insulin resistance, where functional/structural impairment of the insulin receptor B submit results from an abnormality of the insulin receptor gene.

Further examples of type A insulin resistance would be Werner Syndrome in women, leprecornism, lipoatrophic diabetes and other lipoatrophies.

In the light of those observations, it is not surprising that conventional antidiabetic therapies (dietary manipulation, oral hypoglycaemics, insulin injections) have been entirely ineffective in the Mendenhall syndrome. Young patients with the Mendenhall and similar rare syndromes are at high risk of death from ketoacidotic coma if their state of chronic and gross hyperglycaemia is further adversely affected by physiological events (e.g. puberty, menstruation) or added pathology (e.g. infection).

IGF-1 has structural similarities to proinsulin. However, its cell receptor is diff rent to that of insulin. IGF has been investigated for its potential

growth-enhancing effects on farmed animals . It has also been admininstered to patients having Laron - type dwarfism (Laron Z. et al. Lancet 1988; 2; 1170-2).

A process for the production of IGF-1, involving synthesis through the use of recombinant DNA technology, is described in EP-A-0219814. The resulting recombinant IGF-1 is identical in terms of its amino acid composition to naturally occurring human IGF-1.

EP-A-0308386 describes a method for improving the regeneration of transected peripheral nerves in mammals and man, for instance following damage by an accident or surgery, which comprises administering IGF-1.
JP-A-63/196524 relates to a permucosal absorptive carcinostatic action regulator comprising (a) a growth factor, such as IGF-1, and (b) an absorption accelerator.

EP-A-0289584 discloses a wound healing and bone regenerating composition which comprises a mixture of purified platelet-derived growth factor and purified IGF-1. The composition may be used in the healing of external wounds in mammals and is said to act by promoting growth of epithelial and connective tissues and the synthesis of total protein and collagen. EP-A-0237514 describes enhancing the growth of mammary parenchyma in mammals by the intra-mammary administration of a mitogenic agent, such as IGF-1.

EP-A-0209331 relates to the extraction of pure bovine IFG-1 and its use as an animal growth promoter.

FR-A-2533438 refers to the use in cosmetic preparations of various growth factors, such as IGF-1, which have been shown to have a mitogenic action on human or animal skin cells. EP-A-0104933 describes a method for growth promotion and feed efficiency improvement which involves the continuous intravenous or subcutaneous administration of IGF-1.

Summary of the Invention

It is an object of the present invention to provide a treatment for insulin-resistant diabetes.

The present invention relates to the therapeutic use of insulin-like growth factor (IGF) for the treatment of type-A insulin-resistant diabetes.

The invention also provides a method of treatment of a patient having type-A insulin-resistant diabetes which comprises the administration of a therapeutically effective amount of insulin-like growth factor.

The invention further provides the use of insulin-like growth factor for the manufacture of a medicament for the treatment of type-A insulin-resistant diabetes.

Insulin-like growth factors are known and occur naturally in the body. Whilst the present invention is primarily concerned with IGF-1, IGF-2 (which is about ten times more potent) may also be employed. The IGF may be made using recombinant DNA techniques in view of its more ready availability. The IGF protein structure may be

identical to the native product or differ from it by additions, deletions or replacements which leave unaffected its cell receptor binding properties and glucose-reducing effect.

The IGF is usually administered intravenously, subcutaneously or intramuscularly in a dosage such as to provide a target blood plasma level of 50 - 150 micrograms per kg. This intravenous injection is usually at a nominal dosage rate of 3-6 mg/kg body weight. By analogy to known dose-response relationships for insulin, corresponding dosages for subcutaneous and intramuscular administration can be derived. Since IGF has a short halflife in-vivo, administration by intravenous injection may need to be repeated several times a day. Subcutaneous injection has a more extended duration and may be administered less frequently e.g. twice daily.

The IGF may be formulated for extended release by combination with suitable agents (haptens, zinc etc) conventionally used for insulin.

Referred Embodiment

An embodiment of the present invention will now be described by way of example only.

CASE REPORT

The patient was the second child of healthy non-consanguineous parents and was born at 44 weeks'

gestation aft r an uneventful pregnancy. He weighed 2.5kg. at birth and was noted to have abdominal distension, an enlarged phallus and facial dysmorphism. Diabetes mellitus was diagnosed at age 7 years and initial treatment, by dietary/carbohydrate restriction, was unsuccessful. Subsequent therapeutic trials of an oral sulphonylurea (Tolbutamide) and a biguanide (Metformin) were equally ineffective. The injection of subcutaneous insulin (up to 100 units per day) had no appreciable effect on either mean daily blood glucose or glycated haemoglobin level (14.2%, laboratory normal 8%).

By the age of 13 years, he had an established metabolic pattern of gross, chronic hyperglycaemia and intermittent ketonuria. The patient's endogenous levels of IGF-1 were subnormal for his age.

METHODS

Plasma insulin and C-peptide were measured using standard radio-immunoassay (RIA) procedures described previously (1). Plasma IGF-1 was measured using the RIA kit supplied by Nichols Institute Diagnostics, San Juan, California; serum growth hormone was determined using an in-house immunoradiometric assay standardised against the First International Reference Preparation of human growth hormone (MRC 66/217; 2 mu = 1 ug). Insulin binding status was assessed by platelet binding techniques (2,3). IGF-1 was donated by the Fujisawa Pharmaceutical Company,

synthesised by recombinant DNA technology and had an aminoacid sequence identical to that of native human IGF-1 (4). Lyophilised IGF-1 was dissolved in normal saline and injected as a single intravenous bolus of 3 mgm (100 ug/kg) after breakfast. Venous blood was withdrawn for analysis through an indwelling catheter at 0, 2, 5, 15, 30, 60, 120, and 180 minutes after injection. further boluses of 6 and 12 mgm respectively were subsequently given in the fasted state with hormonal profiles measured after the latter dose. A further experiment was performed with a 12 mgm intravenous bolus of IGF-1 given before breakfast and followed by hourly hormonal sampling until 5 p.m. For purposes of comparison, the hormonal response to standard meals was measured and a 75 G oral glucose tolerance test was performed after an overnight fast.

RESULTS

Initial IGF-1 level prior to therapy was subnormal at 0.2 ku/1 (normal 0.5 to 4.0 ku/1, corrected for sex and age). Insulin binding status was examined and found to be impaired (Table 1). Oral glucose tolerance testing (75 G load) confirmed marked hyperglycaemia with gross hyperinsulinaemia (Table 2). Following a 3 mgm intravenous bolus of IGF-1, given post prandially, blood glucose fell to a nadir of 11.2 mmols/1 after 120 minutes (Figure 1). Plasma insulin declined rapidly from 1290 to 315 mu/1 (Figure 3), C-peptide from 1.92 to 0.88 nmols/1

and HGH from 11.2 to 0.5 mu/1 (Figure 2). Also given for comparison is the response to a placebo (intravenous isotonic saline bolus) in insulin, C-peptide, HGH and blood glucose following a standard hospital breakfast (carbohydrate content 50 G). Similar findings were observed following a 6 mgm intravenous bolus; and after a 12 mgm bolus, given in the fasting state, blood glucose declined to 8.3 mmols/1. Thereafter boluses of 12mgm IGF-1 were given intravenously before breakfast and lunch: mean blood glucose over an 8-hour period was 17.4 mmols/1 and mean plasma insulin 290.2 mu/1. By comparison, a mean blood glucose of 29.1 mmols/1 and mean plasma insulin of 769 mu/1 was observed over the same time period when no therapy was given.

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4. Niwa M, Sato S, Saito Y et al. Chemical synthesis, cloning and expression of genes for human somatomedin C (insulin-like growth factor 1) and 59Val-somatomedin C. Ann NY Acad Sci 1986; 469: 31-52.

TABLE 1

Insulin concentration in supernatant (ng/ml)	Specific insulin binding ($pg.2x10^8$ platelets)	
	PATIENT	CONTROLS
0.1	0.27	0.37 ± 0.09
0.2	0.35	0.62 ± 0.17
0.6	1.48	1.70 ± 0.45
1.0	1.48	2.73 ± 0.83

Insulin receptor status (insulin binding) of platelets from patients and controls determined by in vitro assay.

TABLE 2

Time (min)	Glucose	HGH	Insulin	C-peptide
0	11.7	0.9	407	2.3
30	18.9	0.6	510	5.5
60	30.1	0.5	1600	10.2
90	29.9	0.7	934	4.1
120	24.4	6.9	726	3.9

Blood glucose and hormone levels after oral glucose loading (75g), following an overnight fast. Glucose in mmol/l; HGH and insulin in mU/l; C-peptide in nmol/l.

CLAIMS

1. The therapeutic use of insulin-like growth factor (IGF) for the treatment of insulin-resistant diabetes.

2. A method of treatment of a patient having insulin-resistant diabetes which comprises the administration of a therapeutically effective amount of insulin-like growth factor (IGF).

3. A method/use according to claim 1 or 2 for the treatment of type A insulin resistant diabetes.

4. A method/use according to claim 1 or 2 for the treatment of mendenhall's syndrome.

5. A method/use according to claim 1 or 2 for the treatment of Werner Syndrome, leprecornism, Lipoatrophic diabetes and other lipoatrophies.

6. A method/use according to claim 1 or 2 which employs IGF-1.

7. A method/use according to claim 1 or 2 which comprises administration of IGF such as to provide a target blood plasma level of 50-150 micrograms per kg.

8. A method/use according to claim 1 or 2 which comprises administration of IGF at a dosage rate of 3-6 mg per kg body weight.

9. The use of insulin-like growth factor (IGF) for the manufacture of a medicament for the treatment of insulin-resistant diabetes.

10. A sustained release pharmaceutical formulation which comprises insulin-like growth factor (IGF) together with suitable sustained release formulation adjuncts.

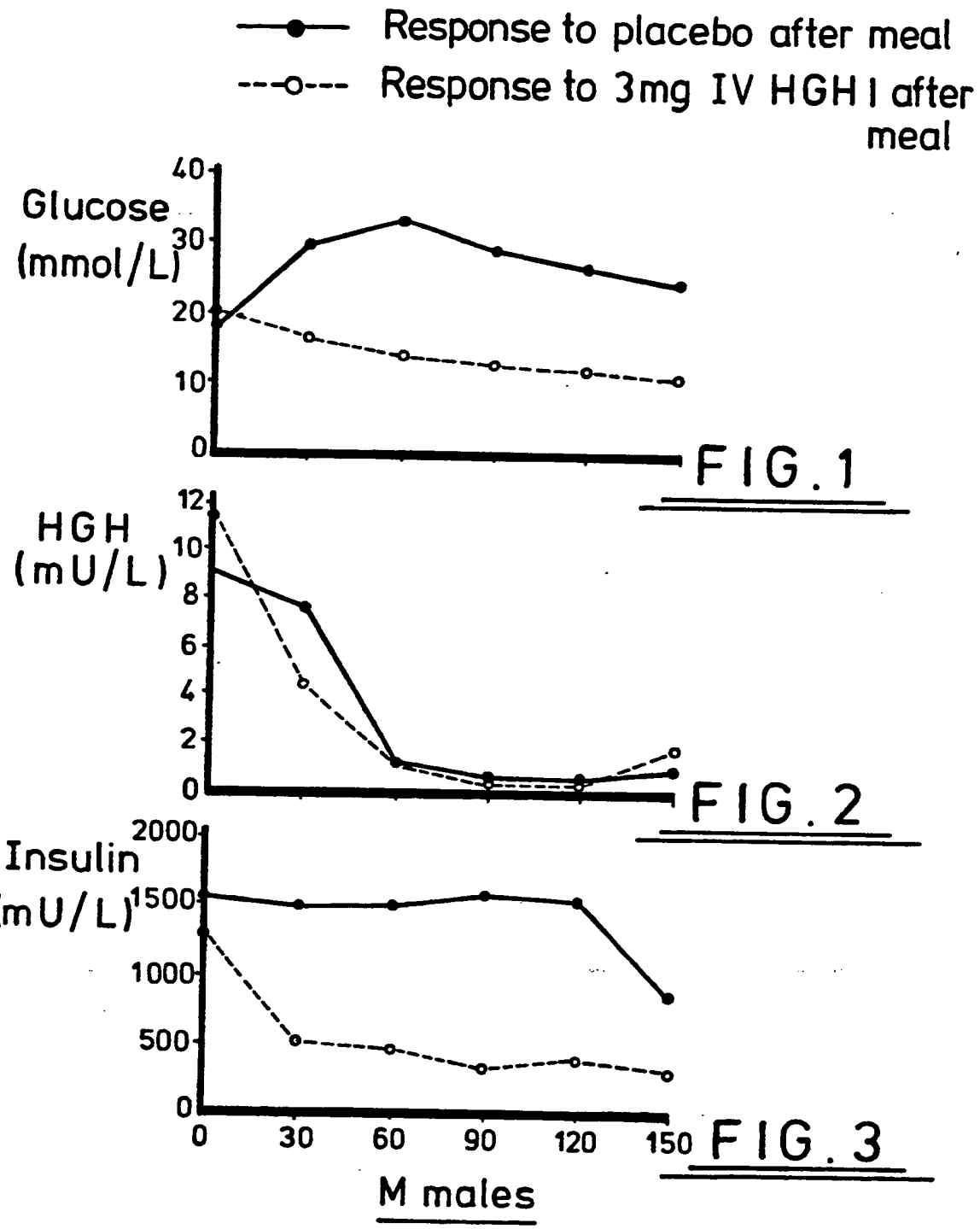

FIG. 1

FIG. 2

FIG. 3

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 90/01399

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: A 61 K 37/36

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	A 61 K, C 07 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	EP, A, 0331630 (CIBA-GEIGY) 6 September 1989 see the whole document	9-10
X,P	EP, A, 0360411 (KABIVITRUM AB) 28 March 1990 see the whole document, especially columns 6-8 "Biological activity"	9-10
Y	The New England Journal of Medicine, volume 317, no. 3, 16 July 1987, H.P. Guler et al.: " Short-term metabolic effects of recombinant human insulin-like growth factor I in healthy adults", pages 137-140 see the whole article	9-10

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* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
7th December 1990	31. 12. 90
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Maria TORIBIO

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FURTHER INFORMATI N CONTINUED FROM THE SEC ND SHEET

Y	Diabetologia, volume 31, 1988, Diabetologia Springer-Verlag, Pub., N. Livingston et al.: "Characterisation of insulin-like growth factor I receptor in skeletal muscles of normal and insulin resistant subjects", pages 871-877 see the whole article	9-10

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers ....*.... because they relate to subject matter not required to be searched by this Authority, namely:

*- claims 1-8
see PCT- Rule 39.1(IV) methods for treatman of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claim numbers ....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9001399 SA 40121

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0331630	06-09-89	AU-A- 2899989	10-08-89
		JP-A- 1233227	19-09-89
EP-A- 0360411	28-03-90	AU-A- 4051889	23-03-90
		WO-A- 9002198	08-03-90

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82